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ScienceDirect
Journal of Forensic and Legal Medicine 15 (2008) 388–390
JOURNAL OF FORENSIC AND LEGAL MEDICINE
www.elsevier.com/jflm

Case Report

Fatal intoxication with milnacipran

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Received 17 September 2007; received in revised form 7 November 2007; accepted 13 December 2007
Available online 11 March 2008

Abstract

The antidepressant milnacipran is a double serotonin/noradrenalin reuptake inhibitor. The low reported incidence of intoxication indicates excellent tolerance in comparison with tricyclic and second generation antidepressants. We report a fatal intoxication associating milnacipran, at blood levels (femoral = 21.5 mg/l, cardiac = 20 mg/l) 40-fold higher than the usual treatment concentration, and six other molecules (fluoxetine, norfluoxetine, sertraline, cyamemazine, nordazepam and oxazepam) at therapeutic levels. To the best of our knowledge, this is the first reported fatal intoxication involving milnacipran.

Keywords: Milnacipran; Forensic toxicology; Autopsy; Suicide; Intoxication

1. Introduction

The antidepressant milnacipran is a double serotonin/noradrenalin reuptake inhibitor. Its lack of affinity for other post-synaptic receptors gives it better cardiovascular tolerance than tricyclic and more recent antidepressants.[1,2] Taken orally, its pharmacokinetics is characterized by rapid intestinal absorption with 85% bio-availability, low protein binding and metabolization and mainly renal elimination as parent drug or glucuronide. The free form of the parent drug is the only active form at therapeutic concentrations. These features prescription well-controlled, combined with the low inter-individual variation in plasma level, low risk of drug interaction and limited impact on the hepatic cytochrome P450 system.[3,4] The only adverse events seen more frequently than with placebo were gastrointestinal symptoms, dysuria, palpitations, and hypotension when associated with phenothiazine.[5,6] A high-concentration emetic effect limits the risk of oral overdose.[7] Three cases of voluntary intoxication have been reported. In the first, a 950 mg dose (9 times greater than the recommended daily dose) caused simple sleepiness, treated by activated carbon and osmotic diuresis; the only complication was amenorrhea–galactorrhea observed at 3 days.[8] The second case involved a 0.334 mg/l milnacipran blood concentration in combination with 1.33 g/l alcohol, again leading to isolated somnolence with favorable evolution under simple surveillance.[9] The last case was a severe multi-drug intoxication causing isolated consciousness impairment, with a Glasgow coma score of 5; the milnacipran concentration as measured by the semi-quantitative BIORAD REMEDI method was 3 mg/l with an estimated

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doi:10.1016/j.jflm.2007.12.006

intake of 1.4 g, the associated psychotropes including a toxic concentration of 172 mg/l meprobamate.[10] Fifteen attempted intoxications have also been reported,[1] with quantities up to 2.8 g milnacipran; few clinical details were provided, except in two cases.[9] The first involved an intake of 1 g milnacipran with a plasma concentration of 0.735 mg/l; the sole symptom was vomiting. The other case presented a plasma concentration of 1.600 mg/l for an intake of 700 mg milnacipran; the victim showed somnolence and sinusal tachycardia, once again with systematically favorable clinical evolution. To the best of our knowledge, the present report is the first of a fatal intoxication by milnacipran.

2. Case report

The victim, a 42-year old woman, was found by passers-by, lying dead on the back seat of her car. The police found empty blister-packs of anetholtrithione, bromazepam, chlorazepate, heptaminol, prazepam and venlafaxine in the car, along with a 1.2 l plastic bottle with 0.2 l of whitish liquid left in it, on the floor of the car. Autopsy was performed the day after the corpse was found. External examination found ungual cyanosis, posterior lividity, and no signs of violence. Internal examination found a slight mitral prolapse, polyvisceral congestion, 20 g of whitish substance in the stomach, and a full (800 ml) bladder.

3. Experimental

Toxicological screening on blood collected from the femoral vein and cardiac cavity was performed by using liquid chromatography with photodiode array detection (HPLC/DAD) and gas chromatography with mass spectrometry detection (GC/MS) as previously described.[11] One milliliter blood spiked with phenazine (750 ng) as internal standard, was extracted by using Toxitube A™. For HPLC/DAD analysis, the dry residue was dissolved in 100 µl HPLC initial mobile phase (described bellow) and 60 µl were injected. The HPLC chain was an Agilent serie 1100. The analytical column was a 250 × 4.6 mm ID Uptisphère C8 Interchrom, 5 µm particle size. The solvent gradient program, composed of a mixture of acetonitrile/phosphate buffer 50 mmol, pH 3.6 was as follow: initial acetonitrile was held at 15% for 2 min, linearly increase to 65% for 13 min and to 80% for 10 min. The identification of the compounds was performed by using the library "UV spectra of toxic compounds" from F. Pragst, M. Herzler, S. Herre, B.-T. Erxleben, M. Rothe (Berlin, Germany 2001). For GC/MS the dry residue was acetylated by using the method described by Maurer[12] and modified as follows: 200 µl of pyridine/acetic anhydride mixture (40/60, v/v) was added to dry residue for 30 min at 60 °C then evaporated and re-dissolved in 100 µl ethyl acetate, and 1 µl was injected. The GC/MS chain was an Agilent 6890 GC with a mass spectra detector 5973. The column was an HP5MS (length 30 m, 0.25 mm ID, film thickness 0.25 µm). The gas vector was helium at 1 ml/min flow. Temperature injector was 260 °C. The oven temperature gradient program was as follow: initial temperature 90 °C held 1 min linearly increase to 200 °C (20 °C/min) and increase to 300 °C (15 °C/min). The identification of compounds was performed by using four spectra libraries: Wiley, NIST 02, Pfleger Maurer Weber V3 and a home made library. For each detected drugs, quantitation was performed by using same HPLC/DAD technique with multi-point calibration tables build by spiked blank blood. The calibration curve for milnacipran was linear ranging from 0.022 to 2.200 mg/l ($y = 1.9845x - 0.0022$, $r_2 = 0.995$, six calibration points, in triplicate). The intercept was not significantly different of zero (Student's t test). Homogeneity of variances has been confirmed by a Cochran's test along the whole tested range. Repeatability, reproducibility and recovery were tested at two concentration's levels: 0.110 mg/l and 1.100 mg/l. The repeatability's study (each of the both levels of concentration analyzed 10 times) has given variation's coefficients of 6.0% and 7.1% for the low and the high level of concentration respectively. The reproducibility's study (each of the both levels of concentration analyzed 10 times three days consecutively) has given variation's coefficients of 11.7% and 12.3% for the low and the high level of concentration respectively. The mean recovery was 38% and 40% for the low and the high level of concentration, respectively. The limit of detection (LOD, 3 standard deviations from the mean of concentrations measured on 10 blank bloods) was 0.001 mg/l. The lower limit of quantitation (LOQ, 10 standard deviations from the mean of concentrations measured on 10 blank bloods) was 0.002 mg/l.

Blood alcohol concentration was analyzed by headspace gas chromatography with a flame ionization detector (HS/GC/FID). The contents of the bottle found in the car were analyzed using the same techniques.

4. Results and discussion

Tables 1 and 2 show the results for the biological samples and bottle contents, respectively. Blood alcohol tested negative (<0.1 g/l). Police findings in this case pointed to voluntary multi-drug intoxication, as did the autopsy results, the absence of any macroscopic cause of death, and the finding of a full bladder associated with polyvisceral congestion. The hypothesis was borne out by toxicolog-

Table 1
Blood toxicology results

Molecules	Femoral blood (mg/l)	Cardiac blood (mg/l)
Milnacipran	21.5	21
Fluoxetine	0.32	0.27
Norfluoxetine	0.33	0.28
Sertraline	0.19	0.20
Cyamemazine	0.21	0.17
Nordazepam	3.0	2.9
Oxazepam	0.11	0.13

Table 2
Toxicology results for the bottle

	Milnacipran	Sertraline
Plastic bottle (mg/l)	4.0	2.5

ical analysis, which found eight psychotropic molecules in the victim's blood. The concentrations were within the therapeutic range, except in the case of milnacipran, found at 40 times the usual maximum prescribed concentration of 0.5 mg/l,[13] indicating a massive overdose. Cardiac and femoral blood levels were equal for the whole of the detected drugs, ruling out any redistribution phenomenon that might have been the cause of a misinterpretation. Several studies[1,5,6,14] have testified to the safety of serotonin and noradrenalin reuptake inhibitors such as milnacipran. Various points were therefore raised to account for the lethal nature of the present case. The estimated milnacipran intake, based on the volume and concentration of the contents of the bottle was particularly large (4 g). The liquid form of the intake may have induced increased and accelerated absorption as compared to an equal intake in the form of tablets. Moreover, the emetic effect reported with oral overdose in tablet form[7] failed to occur in the present case. These two factors may account for the high blood concentration found. Furthermore, although the associated molecules were found at infratherapeutic doses, it is possible that they boosted the effect of the milnacipran. Thus the association with the phenothiazine cyamemazine may have induced hypotension[5] and that with the benzodiazepines may have disturbed consciousness and caused hypercapnia, as reported for milnacipran doses of between 1.9 and 2.8 g.[7] The pharmacokinetic profile of milnacipran is characterized by an extensive absolute bioavailability (85%), a rapid absorption with a t_{max} of 0.5–2 h, and a poor plasma protein binding (13%).[3] On the other hand, sertraline is slowly absorbed following oral administration with a c_{max} of 5–8 h, it exhibits an extensive first-pass metabolism and a high plasma protein binging (>95%).[15,16] These pharmacokinetics' differences could explain why at the time of death, sertraline's blood concentration was not also very high despite similar concentrations of both drugs in the bottle found in the car.

Taken together, these arguments point to what is to the best of our knowledge the first reported case of fatal intoxication by milnacipran in the literature.

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